CONNOLLY BOVE LODGE & HUTZ LLP
The Nemours Building
1007 North Orange Street
P.O. Box 2207
Wilmington, DE 19899-2207
(302) 888-6316
Francis DiGiovanni (#3189)

MORGAN, LEWIS & BOCKIUS LLP
101 Park Avenue
New York, New York 10178
(212) 309-6000
Brian P. Murphy (*pro hac vice*)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXO GROUP LIMITED Plaintiff, v. TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LIMITED Defendants.	**REDACTED VERSION** **August 4, 2006** Civil Action No. 04-171-KAJ

DECLARATION OF DAVID R. LONG, PH. D., IN SUPPORT OF PLAINTIFF GLAXO GROUP LIMITED'S RESPONSE TO TEVA'S MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT

I, David R. Long, Ph.D., declare as follows:

1. I earned a Bachelor of Science degree in pharmacy in 1971 and a Ph.D. in medicinal chemistry in 1975 from Portsmouth Polytechnic University in the United Kingdom.

I was employed at Glaxo Group Research Ltd., which became part of Glaxo Wellcome plc, from April 1980 to May 1998 and currently work as a Community Pharmacist in England.

2. I am the named inventor on the patent-in-suit, United States Patent No. 5,068,249 ("the '249 patent") which issued on November 26, 1991 and was assigned to Glaxo Group Limited.

3. I submit this declaration in support of Plaintiff's response to defendant Teva's Motion for Summary Judgment of Non-Infringement.

4. I have read the following documents to refresh my recollection of events in support of making this Declaration:

- U.S. Patent No. 5,068,249 titled Aqueous Ranitidine Compositions Stabilized with Ethanol;
- My July 24, 1985 File Note (G005295-97/Y011638-640, attached as Exhibit 1);
- Excerpts from Teva's brief in support of its non-infringement motion regarding Teva's interpretation of my July 24, 1985 File Note, pp. 7-9, 29 and 32 (D.I. 110) (hereinafter "Brief");
- Zantac® Syrup Project Notebook P590 (G030411-626/Y007455-7669, relevant portions attached as Exhibit 2); and
- Transcript of my trial testimony from *Glaxo v. Pharmadyne* (Day 1 pages 256-289, and Day 2 pages 403-465, and corresponding exhibits, relevant portions of trial transcript attached as Exhibit 3) (hereinafter "*Pharmadyne* Trial Tr.").

5. My deposition was not taken by Teva in this matter, and I make this declaration to correct the incorrect statements made by Teva in its Brief.

6. During the time period from 1985 to 1986, I was a Research Leader at Glaxo. In that role I led a team responsible for the formulation and development of Zantac® Syrup. My responsibilities included directing and supervising the research and

testing that was performed to resolve a problem with microbiological contamination of Zantac® Syrup by a water-borne bacterium called *Pseudomonas cepacia*. *Pseudomonas cepacia* can contaminate an aqueous drug product, thereby rendering it unfit for human consumption. This research and testing led to my invention that is the subject of the '249 patent.

7. By mid-1985, Glaxo had submitted a Product License Application to the regulatory authorities in the United Kingdom requesting marketing approval for Zantac® Syrup. (*Pharmadyne* Trial Tr. at 279:16 - 281:22, Exhibit 3). During the course of an "in-use" test that simulates how a patient would actually use the product, I and my team detected *Pseudomonas cepacia* in the Zantac® Syrup product prior to its release to the market in the United Kingdom. (*Id.*).

8. My File Note (Exhibit 1) dated July 24, 1985 records my contemporaneous thoughts and efforts with respect to the then on-going investigation into the cause and resolution of the *Pseudomonas cepacia* contamination problem. In this document I record the strategy that I developed to find a solution to the problem. My File Note was then copied by one of my research team members, Janice Wilson, into the Zantac® Syrup Project Notebook P590 (at G030442-45/Y007486-89, Exhibit 2).

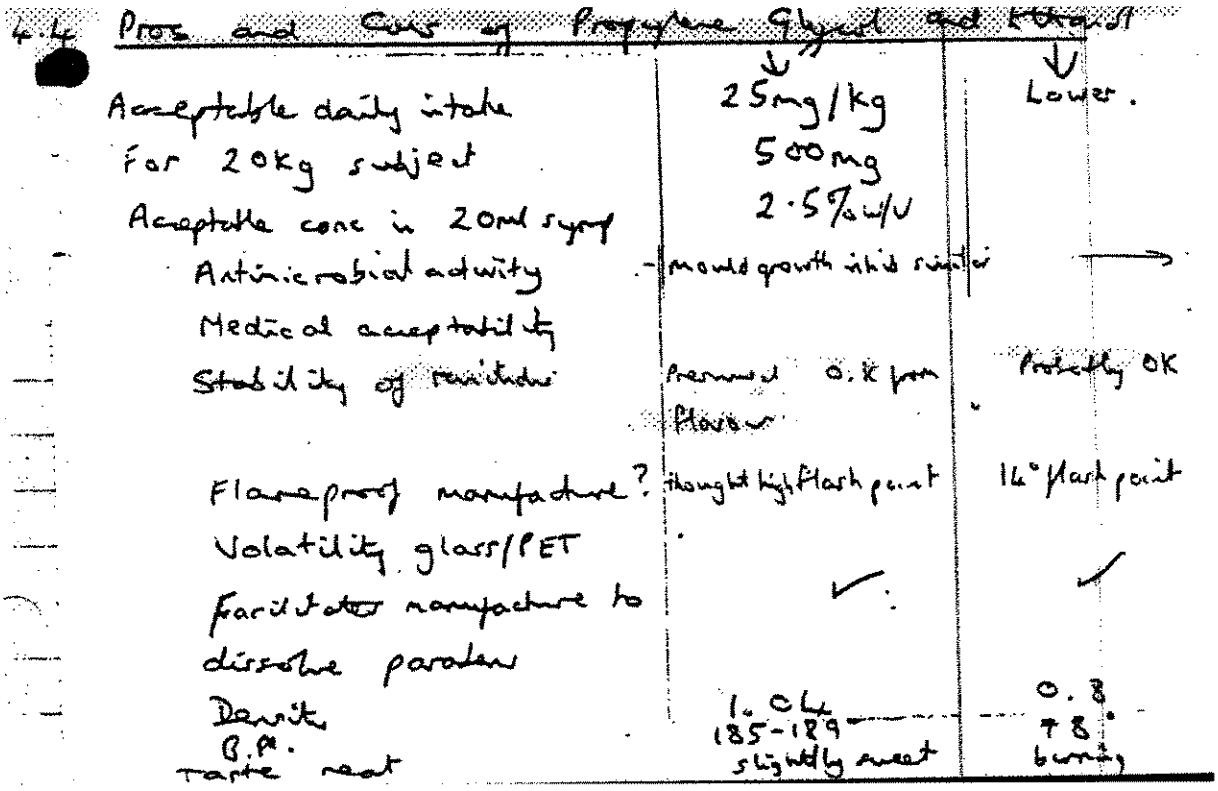
9. Project Notebook P590 documents and records the activities of the Glaxo pharmaceutical development scientists working on the Zantac® Syrup project from approximately July 1985 through October 1986. It was during this time frame that the contamination problem caused by *Pseudomonas cepacia* was examined and solved. I was responsible for directing and supervising the scientists who performed the work and made the entries in Project Notebook P590.

10. I began the search for a solution to the problem of *Pseudomonas cepacia* contamination by considering the possible antimicrobial properties of a number of different excipients. A list of the excipients that I considered is found at Section 5.1 of my July 24, 1985 File Note. (G005297/Y011640, Exhibit 1). I included 5% ethanol, 2.5% propylene glycol, 0.1% phenol and other possible antimicrobial preservatives in this list. I noted that propylene glycol was already a component of the flavouring that was used in the Zantac® Syrup formulation.

11. The protocol set out in Sections 4.1, 4.2, and 4.3 of my File Note for testing Zantac® Syrup formulations containing either 5% (w/v) ethanol, 2.5% (w/v) propylene glycol, or 0.1% (w/v) phenol, provided that formulations containing one of each of these three ingredients were to be prepared for "challenge with *Ps. cepacia*." (File Note at G05296/Y11639, Exhibit 1; Zantac® Syrup Project Notebook P590 at G030442/Y07486, Exhibit 2). This *Pseudomonas cepacia* challenge test would determine whether any of the added ingredients were effective at inhibiting the proliferation of *Pseudomonas cepacia* in Zantac® Syrup. If, and only if, this initial antimicrobial challenge test was successful would further testing then be performed as described in Section 4.1 a), b), c), and d). (*Id.*). The tests described in Section 4.1 c) and d) were stability tests required by the U.K. and U.S. regulatory authorities.

12. In Section 4.4 of my July 24, 1985 File Note (at G005296/Y011639, Exhibit 1; *see also* Zantac® Syrup Project Notebook P590 at G030443/Y007487, Exhibit 2), I comment on the "Pros and Cons of Propylene Glycol and Ethanol." The table found in that section (reproduced below as originally written by me and typed for convenience)

records my thoughts on the possible use of propylene glycol or ethanol as an antimicrobial preservative in Glaxo's Zantac® Syrup product.



4.4 **Pros and Cons of Propylene Glycol and Ethanol**

	↓	↓
Acceptable daily intake for 20 kg subject	25 mg/kg 500 mg	lower
Acceptable conc in 20 ml syrup	2.5% w/v	
Antimicrobial activity	- mould growth inhib similar	→
Medical acceptability		
Stability of ranitidine	Presumed O.K. from flavour	Probably OK
Flameproof manufacture?	thought high flashpoint	14° flashpoint
Volatility glass/PET		
Facilitates manufacture to dissolve parabens	√	√
Density	1.04	0.8
B.P.	185-189	78°
Taste neat	slightly sweet	burning

13. In Section 4.4 of my File Note, with respect to the "stability of ranitidine," I state that the use of propylene glycol was "presumed O.K. from flavour." This comment reflects my thinking at the time that propylene glycol presumably would not negatively affect the stability of ranitidine to a significant extent because propylene glycol was a component of the flavouring that was already being used in the product. Teva is wrong in its assertions that I "considered propylene glycol's function as a stabilizer in an oral ranitidine solution, as opposed to a preservative," that I "assessed … propylene glycol's … effect on the 'stability of ranitidine' " and that I "foresaw the use of propylene glycol as a stabilizer for ranitidine before [my] patent application was filed." (Teva Brief at p. 8). Teva has mischaracterized my File Note and the corresponding entry in the Zantac® Syrup Project Notebook P590.

14. The only test performed on propylene glycol during our investigation of possible solutions to the problem of *Pseudomonas cepacia* contaminating Zantac® Syrup, was to determine whether 2.5% (w/v) propylene glycol in Zantac® Syrup would kill *Pseudomonas cepacia* and preserve Zantac® Syrup against this particular form of antimicrobial attack. The 2.5% (w/v) propylene glycol formulation failed the *Pseudomonas cepacia* challenge test, and we concluded that: "The addition of propylene glycol 2.5% w/v to Zantac Syrup, does not enhance the preserving power of the syrup." (Zantac® Syrup Project Notebook P590 at G030438-39/Y007482-83 and G030521-22/Y07564-65, Exhibit 2 (emphasis in original); *see also Pharmadyne* Trial Tr. at 445:1 - 446:2, G027685, Exhibit 3).

15. To the best of my recollection, and based on my review of the entire Zantac® Syrup Project Notebook P590, I and my project team never considered or tested

2.5% (w/v) propylene glycol for any effect it may have had on the stability of ranitidine. Ranitidine stability studies were not carried out on the 2.5% (w/v) propylene glycol formulation because it failed the initial *Pseudomonas cepacia* challenge test.

16. The protocol set out in Sections 4.1 and 4.2 of my File Note confirms that no further tests on 2.5% (w/v) propylene glycol would have been performed once propylene glycol failed to arrest the growth of *Pseudomonas cepacia*. (Exhibit 1 at G05296/Y011639).

17. My review of the Zantac® Syrup Project Notebook P590 confirms that ranitidine stability testing was performed only on the ethanol formulation and not on the formulation where 2.5% (w/v) propylene glycol was added. (Exhibit 2 at G030525/Y07568 (Stability Batches for the U.K) and G030558-59/Y07601-602 (USA Batches for Stability Testing)).

18. I selected ethanol to be added to the formulation of Zantac® Syrup because of ethanol's effectiveness as an antimicrobial preservative against *Pseudomonas cepacia*. It was only later, after we set up stability studies on the reformulated Zantac® Syrup to measure ranitidine stability over time, that we recognized the surprising ability of ethanol to enhance the stability of ranitidine in an aqueous formulation for oral administration. Propylene glycol had been eliminated from consideration as an antimicrobial preservative long before that time, so it never occurred to me to investigate whether propylene glycol might have the same ranitidine stabilizing effect as ethanol. That is why I did not consider propylene glycol as a possible stabilizing agent for ranitidine.

19. Teva's assertion that I "considered," "foresaw," or "assessed" the use of propylene glycol to enhance ranitidine stability in an aqueous formulation for oral administration is wrong. (Teva's Brief at pp. 8-9, 29 and 32). I never considered or tested whether propylene glycol had any stabilizing effect on ranitidine in an aqueous formulation for oral administration. I did not foresee the use of propylene glycol to enhance ranitidine stability in such a formulation before the December 12, 1986 filing date of my U.K. patent application or at any time thereafter through the time of issuance of the '249 patent on November 28, 1991. Teva's statements to the contrary are wrong.

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct to the best of my knowledge and belief.

Dated: July 25, 2006

D R Long

David R Long, Ph.D.

CERTIFICATE OF SERVICE

I hereby certify that on August 4, 2006, I filed a redacted version of **DECLARATION OF DAVID R. LONG, PH.D., IN SUPPORT OF PLAINTIFF GLAXO GROUP LIMITED'S RESPONSE TO TEVA'S MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT** with the Clerk of Court and will hand deliver such filing to the following:

Josy W. Ingersoll, Esq.
Young Conway Stargatt & Taylor
The Brandywine Building
1000 West Street, 17th Floor
P.O. Box 391
Wilmington, DE 19899

I hereby certify that on August 4, 2006, I have served via Federal Express, the document to the following non-registered participants:

Mark D. Schuman, Esq.
Jeffrey C. Brown, Esq.
Merchant & Gould LLC
3200 IDS Center
80 South 8th Street
Minneapolis, MN 55402

/s/ Francis DiGiovanni
Francis DiGiovanni (#3189)
James D. Heisman (#2746)
CONNOLLY BOVE LODGE & HUTZ LLP
The Nemours Building
1007 N. Orange Street
Wilmington, DE 19801
(302) 658-9141

Attorneys for Plaintiff Glaxo Group Limited

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